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## Cardiovascular Revascularization Medicine



## Pre-Clinical

## Next generation renal denervation: chemical “perivascular” renal denervation with alcohol using a novel drug infusion catheter☆☆☆☆

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## ABSTRACT

**Background/Purpose:** We update the pre-clinical and early clinical results using a novel endovascular approach, to perform chemical renal denervation, via peri-adventitial injection of micro-doses of dehydrated alcohol (ethanol–EtOH).

**Methods/Materials:** A novel, three-needle delivery device (Peregrine™) was used to denervate the renal arteries of adult swine ( $n = 17$ ) and in a first-in-man feasibility study ( $n = 18$ ). In the pre-clinical testing EtOH was infused bilaterally with one infusion per renal artery into to the perivascular space, using EtOH doses of 0.3 ml/artery ( $n = 8$ ), and 0.6 ml/artery ( $n = 9$ ), and with saline sham control (0.4 ml/artery  $n = 3$ ). Renal parenchymal nor-epinephrine (NE) concentration (performed blindly), and safety were the primary endpoints. Data from the first-in-man study ( $n = 18$ ) to evaluate device performance, safety and peri-procedural pain are reported.

**Results:** In the pre-clinical testing renal function was unchanged at 3-month follow-up. Angiography at 90 days ( $n = 34$  arteries) demonstrated normal appearing renal arteries, unchanged from baseline, and without stenosis or other abnormalities. The reductions in mean renal parenchymal NE reductions at 3 months were 68% and 88% at doses of 0.3 and 0.6 ml, respectively ( $p < 0.001$  vs. controls). In the first-in-man study, there was 100% device success, no complications, a mean treatment time of  $4.3 \pm 3$  minutes/artery, and minimal or no patient discomfort during treatment. Angiography at 6-months showed no evidence of renal artery stenosis, and evidence of a reduction of blood pressure from baseline.

**Conclusion:** Perivascular RDN using micro-doses of alcohol is a promising alternative to energy-based systems to achieve dose-dependent, predictable, safe and essentially painless renal denervation. Further clinical evaluation is warranted.

**Summary:** (For annotated table of contents) This paper describes the preclinical results, in a porcine model, and the early first-in-man results, using the Peregrine™ chemical renal denervation catheter to perform renal sympathetic denervation using micro-doses of alcohol.

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## 1. Introduction

In the 1930s–1950s surgical renal sympathectomy was used to treat severe hypertension [1–3]. More recently, catheter-based renal sympathetic denervation has been performed using a point-by-point, monopolar radiofrequency (RF) ablation catheter from the lumen of the renal artery to treat patients [4–11]. This technique has been shown to disrupt renal sympathetic nerve activity [4–7], resulting in significant

and sustained reduction in office-based blood pressure in patients with severe and medically resistant hypertension [4–11].

Despite this early success, the concept of renal sympathetic nerve denervation (RDN) as a means to treat resistant hypertension has been challenged by the recent negative efficacy results from the Symplicity HTN-3 trial [12]. However, before dismissing renal denervation, it is important to understand that there are significant issues with radiofrequency, point-by-point ablation that may limit efficacy and the ability to predictably achieve adequate levels of renal sympathetic nerve denervation. These shortcomings include pain, limited nerve ablation depth [13], a risk of stenosis and intimal thrombus formation related to medial thermal injury [14–18], as well as inconsistent and unpredictable circumferential denervation. Second generation, energy-based, multi-electrode radiofrequency and ultrasound ablation concepts may decrease pain burden and procedure time, but may not resolve the inherent limitations related to thermal injury to the media, depth and adequacy of denervation, and pain [19,20].

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In this context, catheter-based chemical neurolysis, with the selective infusion of a potent neurolytic agent, such as alcohol, into the perivascular (adventitial) space, has the potential to minimize intimal and medial vessel injury while providing circumferential, deep and consistent renal sympathetic denervation. The encouraging short-term results using alcohol for renal denervation in a porcine model were recently reported [21].

The longer-term preclinical studies, presented in this paper, demonstrate that alcohol delivered locally and precisely to the adventitial and peri-adventitial space produces a sustained, profound and predictable reduction in renal parenchymal norepinephrine levels, with histopathological evidence of circumferential, and deep (typically 7–12 mm deep to the intima) sympathetic nerve injury, and with sparing of the normal constituents of the renal artery wall. The early results from the first in man clinical study, presented here demonstrate safety, ease of use, lack of pain, and the feasibility of this approach.

## 2. Materials and methods

### 2.1. Preclinical studies

A novel, three needle-based delivery device, (Peregrine System™, Ablative Solutions, Inc., Kalamazoo, MI) was introduced via the femoral artery into renal arteries of adult swine using fluoroscopic guidance. This drug infusion catheter is an endovascular delivery catheter that contains three distal needles housed within individual guide tubes, which are contained within body of the catheter. The catheter has a steerable, radio-opaque 2 cm fixed, floppy guide-wire at its distal end to minimize renal artery trauma and allow steer ability, when needed, into appropriate branch vessels (Fig. 1).

This study was conducted under the general principles of Good Laboratory Practice (GLP) regulations as set forth in 21 CFR 58. The protocol for this study was reviewed and approved by the IACUC of the test facility, which is accredited by AALAC and licensed by the USDA. Animals were pre-medicated with 325 mg of aspirin and 75 mg of clopidogrel by mouth once daily for 2 days before the procedure.

After the animals were prepared for sterile surgery, one femoral artery was accessed using the Seldinger technique, and a 7 French introducer was placed. Intravenous heparin was given to all animals to achieve an ACT of >250 sec. In all cases the right and left renal arteries

of the pig were engaged using a 7 French RDC-1 guiding catheter. Prior to infusion of either ethanol or saline injections, angiography of each renal artery was performed using iohexol contrast diluted by 25% with normal saline.

The Peregrine™ injection catheter is intended to be used under fluoroscopic guidance by a single-operator using standard endovascular techniques and to allow safe and reproducible fluid injection into the adventitial and peri-adventitial space of a target vessel (Fig. 2). The 0.008" needles that reside within the distal tip of the catheter's guide tubes are advanced to a depth of  $3.5 \pm 0.25$  mm deep to the intima (i.e., beyond the tip of the guide tube) and at 120° separation, one needle to the others. The specialized handle, allows advancement of the three guiding tubes, followed by simultaneous advancement of the three injection needles into the adventitial space. These tiny needles are made radiopaque, so that they can be easily seen under fluoroscopy. The needles are the equivalent of a ~30 gauge needle so that they can be safely advanced through the renal arterial wall without causing bleeding, even after heparin administration [19]. The alcohol (ethanol) is delivered through a luer-lock connector at the proximal end of the handle, resulting in the infusion of the alcohol through the tips of the three needles of the Peregrine™ catheter, and directly into the perivascular, adventitial and peri-adventitial space. This creates a reproducible, deep and circumferential delivery of alcohol to the perivascular space (Fig. 3).

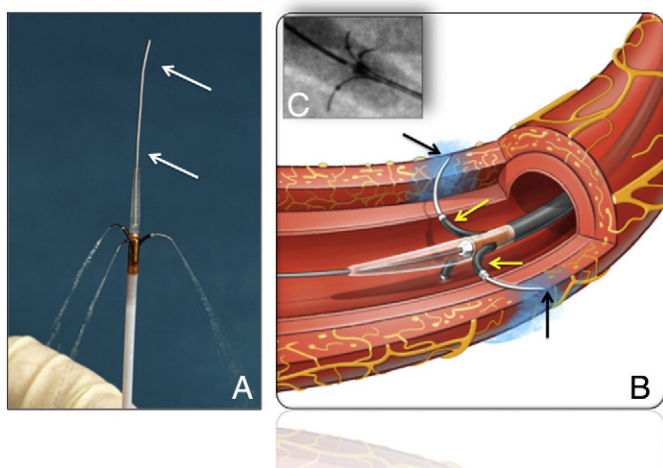
In both the pre-clinical and clinical studies, the successful deployment of the tubes and needles are confirmed by fluoroscopy (Figs. 1 and 2). The radio-opacity of the guide tube tips and of the needles allows visual confirmation of the exact placement of the needle tips and prevents the potential for injection into the lumen. In the porcine study the EtOH or saline (sham) fluid was then administered, using a 1.0 ml luer-lock syringe attached to the proximal injection lumen at the handle of the catheter. The infusion is performed over 1–2 minutes.

Two volumes of EtOH were used in this study: 0.3 ml/artery ( $n = 8$  pigs/16 arteries) and 0.6 ml/artery ( $n = 9$  pigs/18 arteries). A procedural control group was also studied using the infusion of 0.4 ml of saline/artery ( $n = 3$ ). This was a "sham" arm to control for nonspecific effects that might be caused by mechanical injury from either the guide tubes or the needles, and/or any non-specific effects of fluid delivery. Once the treatment agent was infused, the dead space of the catheter was flushed with a very small volume of normal saline (0.1 ml) to clear the dead space and ensure delivery of the agent. After treatment of the first renal artery the device was removed from the animal, inspected and flushed. The contra-lateral renal artery was then engaged, and the same fluid infusion sequence was performed in the contralateral renal artery. After the treatment of the second renal artery, the animals were recovered and housed for restudy and sacrifice at 3-months post-intervention. The animals were treated with aspirin 162 mg/day for seven days after intervention.

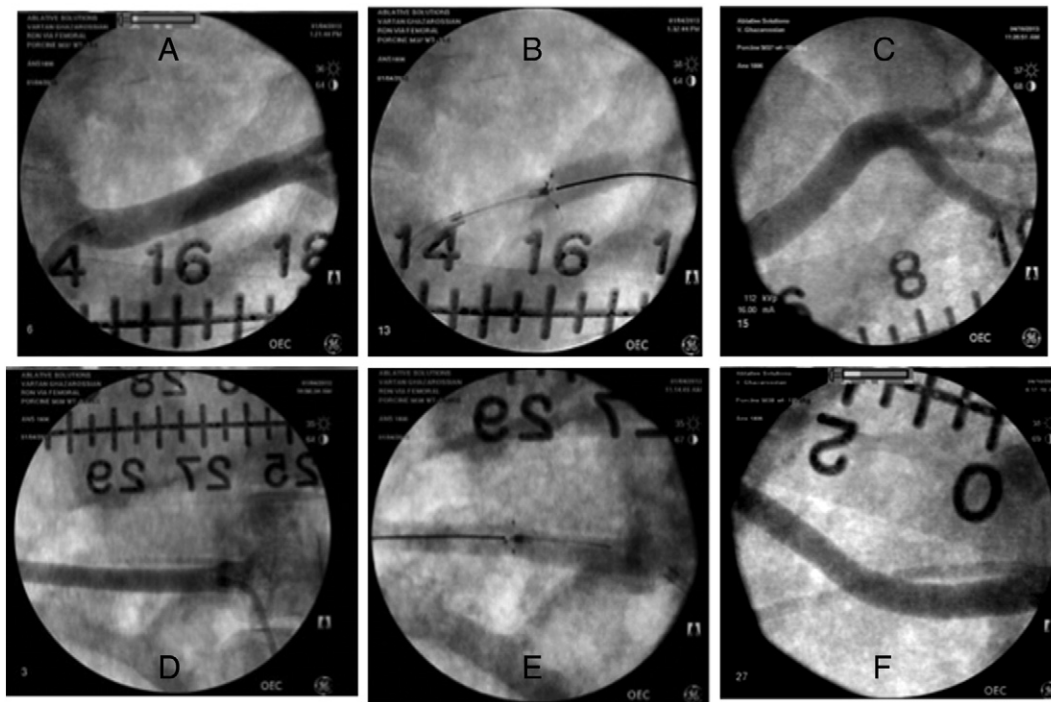
Histopathology was used to evaluate circumferential spread of alcohol by having the pathologist evaluate and document the location (in terms of circumference and depth) of any noted neuritis and neurolysis. The pathologists were blinded as to the treatment (control, alcohol or naïve).

The efficacy of denervation was assessed by measurement of renal parenchymal norepinephrine (NE) levels (analyzed by HPLC, with electrochemical detection), as well as histopathologic evaluation of the perirenal nerves at the end of the three-month sacrifice period. Safety was evaluated by serial blood tests for renal function, 45 and 90-day angiographic studies, and histopathologic evaluation of the renal artery and kidney. At the end of the study period the animals were anesthetized, and angiography of the treated right and left renal arteries was performed to evaluate vessel patency and to look for any luminal narrowing, or other abnormalities as compared to baseline angiography. Evaluation of the angiograms was conducted in a blinded fashion by the angiographic core lab.

After angiographic follow-up a necropsy was performed. The renal arteries and kidneys were harvested for histopathological evaluation.



**Fig. 1.** Images of Peregrine™ device. In panel A the actual device is shown in the deployed state with the guide tubes and needles opened at 120° one to the other and fluid being injected from the handle to the tips of the needles. White arrows show the flexible fixed-wire tip. Panel B shows schematic of the device deployed in a renal artery with alcohol (blue) being injected into the adventitial and peri-adventitial space. Yellow arrows show deployed guide tubes and black arrows depict tips of deployed needles. Panel C shows the fluoroscopic image of the deployed device with radio-opaque markers at tip of guide tubes and radio-opaque needles.



**Fig. 2.** Angiography of renal arteries baseline, during deployment of the Peregrine System™, and at 90-day follow-up. A and D show the pre-treatment renal arteries. Panels B and E show the angiographic image of the Peregrine System™ at the time of infusion. Panels C and F show 90-day angiographic findings in these two animals treated with 0.30 ml EtOH. There is no detectable luminal narrowing or other abnormality.

Gross pathology to examine the status of the renal arteries was performed to look for renal artery abnormalities such as aneurysms, perforations, dissections, hematoma, etc., as well as inspection of the surrounding tissues for any abnormalities. The renal arteries were cannulated, flushed and perfused with formalin while in-situ. The renal arteries and the kidneys were harvested, retaining the peri-adventitial tissue around the artery. The renal artery tissue was embedded in paraffin using standard techniques. Each renal artery was evaluated in at three locations; proximal, mid and distal. Tissue was stained with H&E and Movat's pentachrome. Microscopic evaluation was conducted in a blinded fashion.

Prior to euthanasia of each animal, the kidneys were isolated, and four samples were obtained from random locations at each of the proximal, mid and distal regions of each kidney for a total of 12 samples/kidney. The tissue samples were weighed, placed in cryovials and flashed frozen by immersion into dry ice. The frozen samples were then stored at  $-70^{\circ}\text{C}$ . They were sent in dry ice to an independent laboratory for (blinded) measurement of renal parenchymal norepinephrine levels.

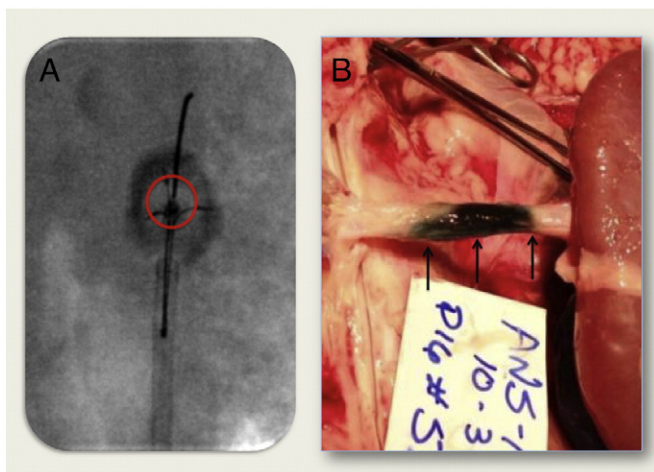
Renal norepinephrine concentrations in the treated animals from this study were also compared to values from naïve control animals of the same age and species ( $n = 8$ ) with renal tissue sampling performed in an identical fashion to the treated animals.

## 2.2. First-in-Man Study

The protocol for this study was approved by the local ethics committee (Republic of Paraguay) and conducted in accordance with local regulations and statutes. Patients were enrolled in the study only after giving written informed consent. This was a pilot study performed in patients with refractory or "resistant" hypertension, using the same definition of refractory hypertension, as defined in the Symplicity studies [12]. Patients were enrolled after careful screening and a 4-week run in period to measure serial office-based BP. All study patients were treated with maximally tolerated doses of at least three antihypertensive medications.

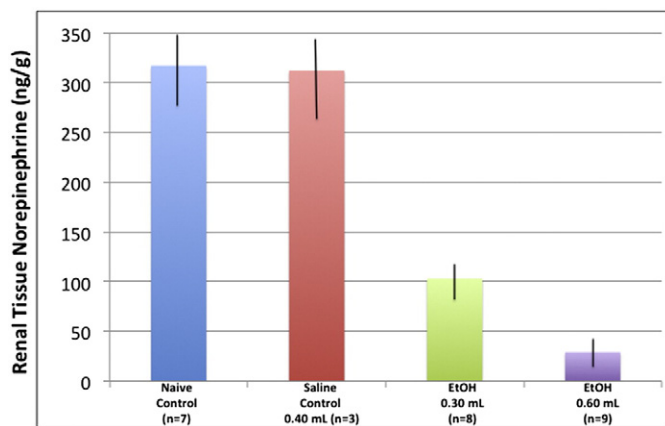
Eighteen patients were enrolled in the study and underwent bilateral renal artery denervation using the Peregrine™ device with a dose of 0.3 ml/artery. Only modest conscious sedation was used such that pain scores could be assessed during the alcohol infusions. Pain was assessed using a standard numeric pain rating scale (0 = no pain; 10 = severe pain) scoring system using verbal interaction with the patient in real-time at the time of start of the infusion and then repeated every 60 seconds after the infusion, until the complete resolution of pain (0/10).

Patient safety was assessed by serial measurement of BUN, Cr, and eGFR and by follow-up bilateral renal angiography at 6-month follow-up. Office-based BP was measured prior to intervention ( $\times 2$ ) and then



**Fig. 3.** Evidence of circumferential delivery and axial distribution of fluid after infusion with Peregrine System™. In panel A, a lateral view is shown in a porcine model after injection of 0.4 ml of contrast plus + saline. Red circle illustrates location of media. This demonstrates the circumferential distribution of fluid delivery in the adventitia from the three needles of the Peregrine System™ at the time of injection. Panel B shows the gross pathology shortly after the injection of 0.15 ml of ethanol admixed with 0.15 ml methylene blue, showing circumferential spread with as well as ~1.5 cm long axial spread.





**Fig. 4.** Bar graph showing the dose-response effect of adventitial EtOH delivery upon renal parenchymal norepinephrine level at 90 days. There is a marked and dose-dependent reduction of NE levels versus both naive control animals and sham control animals injected with saline. Mean NE reduction was 68% with 0.3 ml (n = 8) and 91% using 0.6 ml/artery (n = 9). Standard deviation (SD) for each data set as shown.  $P < 0.001$  for both 0.3 ml/artery and 0.6 ml/artery treatments vs. both naive and sham (saline) controls.

at one-month, 3 months and at 6-months after denervation. Medication compliance was challenging in this study due to the demographics of this patient population studied, and a language barrier.

For statistical analysis, between-group comparisons were made using a Wilcoxon rank-sum test, performed in R (Version 2.14.1, Vienna, Austria). Data are shown in graphs as mean  $\pm$  SD. A p value of  $<0.05$  was considered significant.

### 3. Results

#### 3.1. Preclinical results

Device success was defined as successful infusion of the designated fluid without serious adverse events. In the porcine experiments the device was used successfully in all 20 animals and 40 renal arteries. Procedure time, measured from the advancement of the device into the renal artery, followed by deployment of tubes, then needles, injection, flushing, retraction of needles and tubes, and withdrawal back into the guiding catheter averaged approximately 90 seconds for each renal artery. There was no study-related morbidity or mortality. There were no cases in which the anatomy precluded successful device delivery. There were no dissections, perforations, extramural hematomas, thrombus formation or other device-related complications. Mild to moderate spasm was noted in some of the arteries but appeared to resolve slowly during limited observation, did not impair antegrade renal blood flow, and was completely absent at 45 day and 3-month follow-up.

Measurements of renal tissue NE showed a highly significant, and dose-related reduction in renal parenchymal NE levels at three months, comparing both the 0.3 ml/artery-treated animals ( $p < 0.001$ ) and the 0.6 ml/artery-treated animal ( $p < 0.0001$ ) vs. the sham treated and true (untreated) controls. The mean renal NE reductions were 68% and 88% at doses of 0.3 ml/artery, and 0.6 ml/artery, respectively ( $p < 0.001$  vs. combined controls) (Fig. 4).

Angiographic follow-up of all the 32 alcohol-treated vessels at 90  $\pm$  5 days showed no evidence of renal artery narrowing at EtOH doses of 0.3 or 0.6 ml/artery (Fig. 2C, F). There were no other abnormalities noted, including no aneurysmal changes or thrombus.

Histological examination revealed marked, deep, and circumferential renal nerve injury at depths of up to 13.4 mm from the intimal surface (Fig. 5). There was no discernible nerve injury in the sham animal, infused with saline (Fig. 5C, D). Nerve injury in the EtOH-treated vessels was characterized by vacuolization, loss of internal architecture, and the development peri-neural fibrosis (Fig. 5B). Nerve injury appeared

permanent and with damage to the perineural sheath that would prevent nerve regeneration.

Histopathology revealed no evidence of device-related or EtOH-induced injury to the intimal layer of treated vessels (Fig. 5A). There were no thrombi, dissections, aneurysms, perforations, hematomas, neointimal formation, negative remodeling or other device-related pathology.

At both 0.3 and 0.6 ml/artery doses there was occasional, focal pallor of some smooth muscle cells in the outermost layer of the media, typically originating at the adventitial surface and in close proximity to the injection sites. At some of these sites there was focal proteoglycan deposition. Inflammatory responses were absent at 3-months, and the vessels appeared to be healing normally, without evidence of fibrosis. There was no evidence of negative remodeling observed in any treated vessel. There was no discernible collateral injury to tissue deep to the peri-adventitial plane, including the kidney, adrenals, bowel, etc. There were no adverse nephrotoxic or systemic effects seen. The pigs' serum creatinine, BUN and electrolytes remained within normal and expected limits over the study period.

#### 3.2. First in man

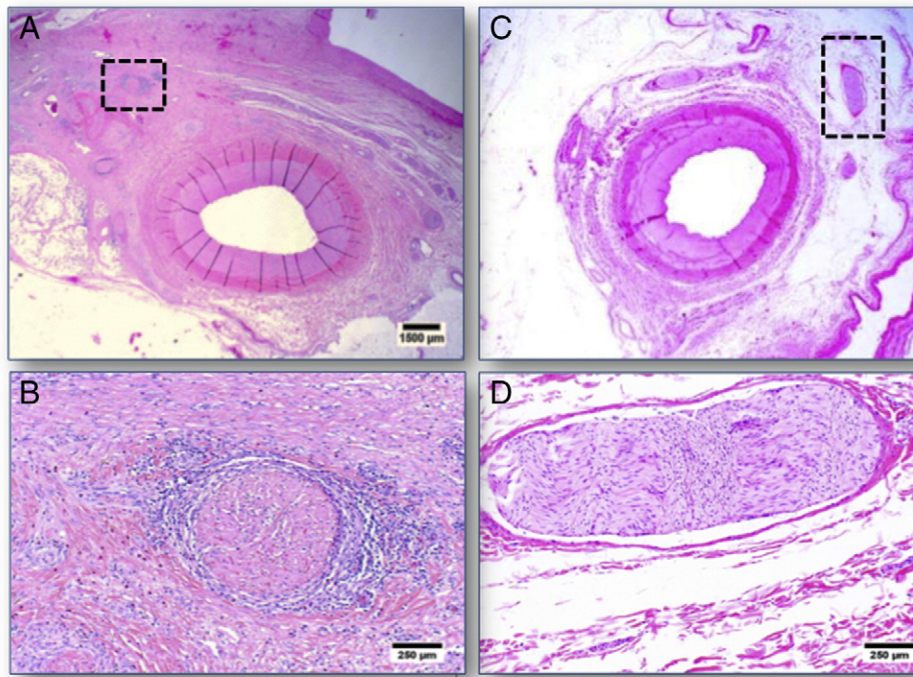
All 18 patients were treated successfully with bilateral renal denervation using the Peregrine device. One patient had a relatively large accessory renal artery (~5 mm diameter), which was treated in addition to the main renal artery. Thus, a total of 37 renal arteries were treated in the FIM experience. Device success was 100%, and there were no acute adverse events noted. Specifically, there was no significant bleeding, spasm, thrombus formation, dissection, slow flow, or other adverse events observed.

The patients tolerated the procedure well with minimal conscious sedation (Midazolam 5 mg & Fentanyl 50  $\mu$ g). Patients were queried during the alcohol injection and were asked to rate their discomfort/pain on a 0–10 scale. The majority of infusions were performed with the patients reporting no pain (23 infusions or 62%). Mild pain (score of 1–3) or moderate pain (score of 4–6) was reported during 6 infusions (16%) each. Severe pain (score of 7 to 10) was reported during 2 infusions (5%). The discomfort/pain was transient, with no pain being reported within 1–2 minutes after the infusion. With slower infusion rates (60–90 seconds) no pain was observed in the final 8 patients.

Follow-up at 3 and 6-months demonstrated excellent renal safety, with no change in BUN, Cr, or eGFR. No other trends were recognized in the remaining clinical chemistry values. One patient expired at 9 weeks (67 days) post treatment during hospitalization for a vascular-related mesenteric infarction. Corrective surgery was performed, but the patient developed septic shock and death. This significant adverse event was reviewed by the principal investigator, and was determined to be unrelated to either the Peregrine device or procedure. One patient was lost to follow-up after the 3-month evaluation.

All remaining 16 patients had follow-up bilateral renal angiography at ~6 months post-intervention. A core lab performed post-hoc, blinded assessment of the angiographic images from the procedures, and follow-up angiography. No patient had any renal artery abnormality at follow-up. The renal arteries were unchanged from baseline. There were no vessels with any narrowing of  $>10\%$  diameter stenosis at the treatment site (n = 32 renal arteries) (Fig. 6).

The vast majority of patients, 88%, who were evaluated had a reduction in blood pressure from baseline to the 6-month time point. There was a mean reduction of  $-27 \pm 5$  mmHg (systolic), and  $-12 \pm 4$  mmHg (diastolic BP) among the 16 patients at 6-month follow-up. This reduction in blood pressure occurred while the majority of patients reduced the number of anti-hypertensive medications they were taking (mean  $-1.2$  medication reduction per patient). No patient in this trial required an increase in the number of anti-hypertensive medications. A number of the patients had substantial BP lowering in the face of substantial reduction of antihypertensive medications



**Fig. 5.** Histopathology (H & E) of renal denervation at 14 days with 0.3 ml EtOH injection (A and B) vs. sham control (C and D). The renal artery (intima and media) appear intact without evidence of injury or inflammation. The reaction to the EtOH is circumferential and limited to the adventitial layers (A and B). There is no apparent damage to the nerve fibers in the saline-injected sample (C and D).

(Fig. 7). The more detailed data of the first-in-man study are being reviewed, and prepared as a separate manuscript and are not within the intended scope of this review.

#### 4. Discussion

Hypertension is a common condition associated with significant morbidity including stroke, heart failure, myocardial infarction, renal failure, and reduction in cardiovascular events. Importantly, observed morbidity and mortality in patients with poor BP control is significantly higher than in those patients in whom blood pressure can be well controlled. Therefore, alternative methods to supplement medical therapy have been explored as early as the 1930s [1–3].

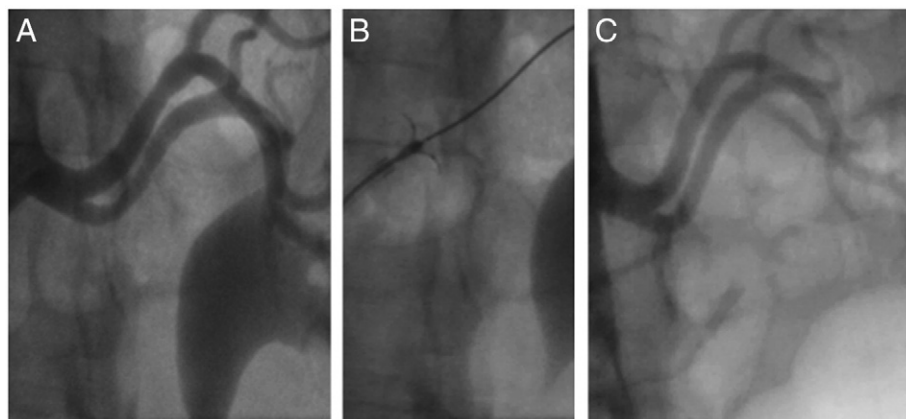
Renal sympathetic nerve denervation, using primarily radiofrequency (RF) mediated “thermal injury” to denervate the renal arteries in humans has shown early evidence of efficacy in lowering blood pressure

in patients with “refractory” hypertension [4–11]. Second generation RF devices have also demonstrated efficacy and safety in BP lowering [19,20].

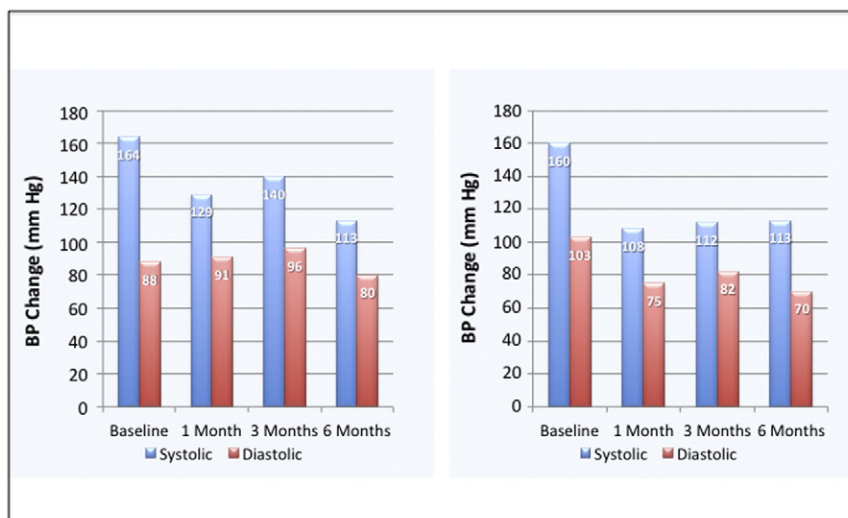
Endovascular radiofrequency (RF) energy application with a unipolar single electrode catheter has been accompanied by significant office-based blood reductions and important, but smaller ambulatory blood pressure reductions in both uncontrolled studies, and in a randomized non-blinded trial [4–7].

More recently, the negative results from the randomized, sham-controlled Medtronic Symplicity-HTN 3 trial [12] have left some casual observers skeptical about the promise of renal denervation as a means to manage hypertension.

However, some experts in the field have begun to shed light on the potential causes of the trial's failure. It has become increasingly clear that one of the problems with RF-mediated renal denervation is poor efficacy related to the treatment procedure leading to unpredictable,



**Fig. 6.** Angiographic images from first-in-man study. Anatomically challenging, short (9.8 mm long) main-stem, left renal artery, treated easily with Peregrine™ catheter which requires only a very short “landing zone” to deliver circumferential chemical renal denervation (panel A). Panel B shows deployment of Peregrine™ catheter. Figure C shows the 6-month angiographic follow-up with no lesions or narrowing. 32/32 renal arteries treated in this study were normal and unchanged from baseline at 6-month angiographic follow-up.



**Fig. 7.** Examples of office-based pressure lowering at 1, 3 and 6 months in patients from first-in-man study. In the first patient (graph on left) the patient was taking 4 antihypertensive medications at baseline, with a reduction to 3 medication at 3 and 6 months (51 mmHg drop in SBP and 8 mmHg drop in diastolic BP). In the second patient (graph on right) the patient was taking 3 antihypertensive medications at baseline, with a reduction to 1 medication at 3 and 6 months (47 mmHg drop in SBP and 33 mmHg drop in diastolic BP).

incomplete and inconsistent sympathetic nerve injury, and “inadequate denervation.” [13,22]. “Non-responders” are not necessarily unresponsive to renal sympathetic denervation. They may just be inadequately denervated [22].

RF-based ablation from the intima, in a point-by-point, or even multipoint array suffers from the number of limitations, including inadequate depth of neurolysis [13]. Porcine studies and a recent human autopsy report suggest that the maximum depth of nerve injury is as little as 2 mm from the intimal surface, and potentially less in diseased arteries [13]. This may lead to the possibility of “missing” more than half of the sympathetic nerves [23,24]. There is also a likely lack of circumferential neurolysis, since each point ablation typically creates only a ~30–40° arc of damage [13]. Thus, with an average of only 3.8 ablations, as was done in the Symplicity HTN-3 trial, one can estimate that as little as 120–160° arc of the renal artery is being treated. With the combined lack of depth and a lack of circumferential coverage, it is likely that 4–6 “burns” may achieve as little as 20–30% denervation in the majority of cases.

The anatomical challenges related to RDN with the RF-based approach are also supported by a recent analysis of the Symplicity-HTN 3 data by Kandzari, et al. [22]. These data show a dose-response to RF, such that patients receiving 4–6 ablations have essentially no BP lowering effect vs. the sham group. BP lowering was not observed until one performed 7–9, or greater, ablations per artery. This may pose a major challenge to the second generation RF “spiral” ablation concept, since a small minority of patients have the 4–5 cm long renal arteries required to safely achieve this threshold number of “spiral” ablations, unless one performs denervation in much smaller, distal branch vessels. This “distal branch vessel” approach has been proposed, but may pose a greater risk of late renal artery stenosis in these smaller (2.5–3.5 mm diameter) branch vessels.

Alternatively, chemical renal denervation, as described in this paper, using micro-doses of dehydrated alcohol (ethanol) has been evaluated in preclinical and early clinical studies. This approach may overcome many of the serious limitations of energy-based denervation.

Alcohol has been well established as an excellent neurolytic agent in a wide range of clinical specialties and may be especially well suited for renal denervation. Even at very low concentrations it may exert a local anesthetic effect. At higher concentrations, as was used in these studies, it causes denaturation of essential cellular proteins, and membrane damage by extraction of phospholipids, cholesterol and cerebroside [25–29]. Damage to the perineural sheath at these doses may also effectively help prevent nerve regeneration.

The Peregrine™ infusion catheter has been extensively tested in a porcine model to deliver micro-doses of ethanol to the adventitia (Fig. 1). This catheter is now FDA 510 K cleared for the infusion of diagnostic or therapeutic agents into the perivascular space. The device's three 0.008” needles are deployed simultaneously, at 120-degrees, one to another at a depth of ~3.5 mm measured from the intima. At this depth the needle tips are located in the adventitia, and thus in very close proximity to the sympathetic nerve fibers. Alcohol doses of 0.3 and 0.6 ml consistently achieve ~65–92% nerve inactivation, as evidenced by drops in renal parenchymal norepinephrine measurements, and by histopathological evaluation. Histopathologic examination after alcohol infusion demonstrates essentially complete, circumferential neurolysis at depths of up to 7–14 mm from the intimal surface [21].

In the early human experience, with 18 patients treated in the first human use study, there were significant BP reductions in the vast majority of patients, typically in the face of a reduction of antihypertensive medications. The delivery of 0.3 ml of ethanol to the adventitia in these patients was also essentially painless, which offers a major advantage over treatment with thermal ablation catheters. Importantly, there was 100% device success, short procedure times, no adverse events and no evidence of renal artery narrowing or other changes at 6-months of follow-up.

Taking the aforementioned limitations of energy-based renal denervation concepts into account, renal denervation by catheter-based perivascular alcohol injection may have a number of advantages. First, tissue injury of the intima and media, that is common to energy-based systems is minimized or eliminated using micro-needles that penetrate 3–4 mm deep to the intimal surface of the renal artery, and with distribution of alcohol limited to the adventitia and perivascular space. Second, uniformly circumferential nerve damage at depths of 7–14 mm is routinely achieved with ethanol injection, providing more consistent and complete denervation. Third, in the absence of medial injury, periprocedural pain is typically essentially absent, thus requiring minimal analgesia and sedation. In addition, there are virtually no limitations to the length of the renal artery that can be treated, and few limitations to the diameter or angle of renal artery take-off (Fig. 6). The procedure is very efficient with a very short procedural time. Finally, no generator or accessory capital equipment is required, thus limiting procedural costs.

## 5. Conclusions

In summary, chemical renal denervation using ethanol may have advantages over energy-based “thermal” technologies, including, an



ability to get predictable circumferential nerve kill at substantial depth, to achieve efficient, complete and predictable denervation with minimal anatomical limitations, and without a need for capital equipment. This approach also allows one to target the nerves where they are located (in the adventitia), and thus minimize injury to the intima and media. Finally, in contrast to RF or ultrasound ablation this approach appears to be essentially painless. Additional clinical evaluations are underway to better define the safety and efficacy of this promising “next generation” technology for renal sympathetic denervation.

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